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**(54) Title:** AMINOTETRALIN DERIVATIVE FOR THE THERAPY OF CARDIOVASCULAR DISEASES**(57) Abstract**

The use of 5,6-diisobutyroyloxy-2-methylaminotetralin in the preparation of pharmaceutical compositions for the therapy of cardiac disorders, particularly of congestive heart failure.

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AMINOTETRALIN DERIVATIVE FOR THE THERAPY OF CARDIOVASCULAR DISEASES

The present invention relates to the use of 5,6-diisobutyroyloxy-2-methylaminotetralin in the preparation of pharmaceutical compositions for the therapy of cardiac disorders, particularly congestive heart failure.

Notwithstanding the therapeutical progresses of the last years, congestive heart failure is still one of the main death causes.

The symptomatic therapy usually aims at reducing the workload of the decompensed heart and improving the mechanical function.

Recently, cardiac failure was proved to be related with important biochemical and neurohumoral changes involving different factors.

In fact, when cardiac output diminishes, compensatory mechanisms act in the body in order to maintain the circulatory homeostasis.

In heart failure, vasoconstriction associated with the activation of said mechanisms cause an increase in peripheral vascular resistances.

As a consequence, the after-load increases which can in turn further strain the already weakened heart, triggering a vicious circle which leads to a progress of the pathology.

This generalized vasoconstriction is mainly caused by the activation of the sympathetic nervous system consequent to the increase of plasma catecholamines, particularly adrenalin, which is an early signal of

cardiac decompensation.

A close relationship between degree of sympathetic activation and severity of the disease seems to exist, and a direct connection between noradrenalin plasmatic levels and mortality seems moreover established.

Therefore, the therapy of congestive heart failure has to be directed to the improvement of the hemodynamic factors, on one hand, and to the pharmacological modulation of the neurohumoral system on the other.

Dopaminergic drugs appear as candidates to become established as drugs for heart failure in the majority of patients.

In particular, dopamine has peculiar characteristics, compared with the other medicaments, since it stimulates both dopaminergic and alpha and beta-adrenergic receptors.

Two types of dopaminergic receptors exist: those located on the smooth muscle of the vascular system ( $DA_1$  receptors) which mediate vasodilation in the renal, mesenteric, cerebral and coronary districts, and those in pre-synaptic position ( $DA_2$  receptors), which inhibit noradrenalin release from post-ganglionic sympathetic nerve endings to blood vessels and heart.

The usefulness of dopamine in the treatment of heart failure is however restricted by it being inactive orally.

Analogously dobutamine, a synthetic analogue of dopamine, can be used only intravenously.

Aminotetralin derivatives have been studied for a long time as dopamine structural analogues for any uses as medicaments.

However, none of these compounds has up to now been introduced in therapy.

One of them, 5,6-dihydroxy 2-methylaminotetralin hydrobromide, was disclosed as coronary vasodilator in 5 the US patent n. 4,134,997 in the name of Joseph G. Cannon.

Cannon administered the compound to dogs at a rate of approximately 10 µg/kg animal weight per minute (range 8.5-13.9) by a continuous intravenous infusion 10 and demonstrated a substantial increase in coronary blood flow.

5,6-Diisobutyroyloxy-2-methylaminotetralin, herein-after referred to as CHF 1035, has been described first in GB Pat. 2123410 among a series of aminotetralin 15 derivatives disclosed as potential antibronchospastic due to their activity on adrenergic receptors.

Both 5,6-dihydroxy-2-methylaminotetralin (herein-after indicated with the experimental abbreviation CHF 1024) and CHF 1035 have been formerly characterized as 20 compounds having prevailing selective activity on  $\beta_2$  adrenergic receptors.

Now it has been surprisingly found that CHF 1024 and CHF 1035, in addition to the already known  $\beta_2$  agonist activity, have remarkable peripheral DA<sub>2</sub> and  $\alpha_2$  25 presynaptic activities leading to a reduction of the sympathetic tone, which is elevated in heart failure patients.

Studies carried out in the animal proved that CHF 1024 and CHF 1035 have a vasodilating activity due the 30 combination of their effects on  $\alpha_2$ ,  $\beta_2$  and DA<sub>1</sub>/DA<sub>2</sub> receptors as well as a cardiac inotropic activity.

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They are effective at a very low doses, even by oral route.

The peripheral  $\alpha_2$  adrenergic and peripheral DA<sub>2</sub> dopaminergic activities of the aminotetralin derivatives of the present invention have never been described until now.

On the contrary, it was previously affirmed by Hilditch A. and Drew G. M. in European Journal of Pharmacology vol. 72, pages 287-296, 1981 that the compound 5,6-dihydroxy 2-methylaminotetralin was inactive as dopamine receptor agonist in relaxing the splenic artery strips.

We have demonstrated that both CHF 1024 and CHF 1035 have agonist activity on dopaminergic receptors and that they are selective for the presynaptic DA<sub>2</sub> ones.

The  $\alpha_2$  adrenergic and DA<sub>2</sub>-dopaminergic activities of the compounds have been evaluated in binding tests (example 1 and 3), in isolated neuronally-stimulated rat vas deferens (example 2) and in rabbit rectococcygeus muscle (example 4).

The cardiovascular effects of the compounds have been evaluated in vivo in anesthetized rats both after intravenous and intraduodenal administration (example 5).

#### 25 Example 1

The affinity of CHF 1024 and CHF 1035 for  $\alpha_2$  adrenergic receptors was tested on human platelets and on rat cerebral cortex.

The antagonist [<sup>3</sup>H]-rauwolscine was used as marker of the receptor, being its binding reversible, saturable and specific.

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CHF 1024 exhibited a significantly higher affinity than dopamine, 9 times in platelets and 15 times in cerebral cortex. The affinity of CHF 1035 was similar to that of dopamine, utilized as reference compound.

5        The lower affinity of CHF 1035 for the receptor is probably due to the esterification of the molecule.

	CHF 1024	CHF 1035	DOPAMINE
human platelets	$3.39 \times 10^{-7}$ ( $\pm 0.13$ )	$2.70 \times 10^{-6}$ ( $\pm 0.45$ )	$3.04 \times 10^{-6}$ ( $\pm 0.38$ )
rat cerebral cortex	$2.62 \times 10^{-7}$ ( $\pm 0.58$ )	$2.65 \times 10^{-6}$ ( $\pm 0.67$ )	$4.06 \times 10^{-6}$ ( $\pm 0.97$ )

10        Values are expressed as  $IC_{50}$  = molar concentration of drug required for 50% inhibition of [ $^3H$ ]-rauwolscine specific binding.

15        Example 2  
The  $\alpha_2$ -adrenergic activity of the aminotetraline derivatives CHF 1024 and CHF 1035 has been evaluated in isolated neuronally-stimulated rat vas deferens in comparison with dopamine.

20        The results are expressed in the following table as  $IC_{50}$  value = molar concentration of drug which induces 50% inhibition of the electrically induced contraction:

	CHF 1024	CHF 1035	DOPAMINE
25 $IC_{50}$ (M)	$2.70 \times 10^{-7}$	$7.14 \times 10^{-8}$	$4.91 \times 10^{-6}$
C.I.	2.15 - 3.38	5.63 - 9.05	4.19 - 5.75
C.I. = 95% Confidence Interval			

25        The compounds CHF 1024 and CHF 1035 resulted about 20 and 70 times more potent than dopamine, respectively.  
30        Example 3 - peripheral DA<sub>2</sub> dopaminergic activity (binding test)

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The affinity of CHF 1024 for peripheral DA<sub>2</sub> dopaminergic receptors was tested on bovine adrenal cortex evaluating its effect on the interaction of [<sup>3</sup>H]-(-)sulpiride with the specific binding sites of this system.

5 Dopamine has been employed as reference compound.

The results, expressed as IC<sub>50</sub> (molar concentration required for 50% inhibition of specific binding) are reported herebelow.

	CHF 1024	DOPAMINE
10 Bovine adrenal cortex	2.1 x 10 <sup>-8</sup>	2.3 x 10 <sup>-7</sup>
[ <sup>3</sup> H]-sulpiride		

The affinity of CHF 1024 for DA<sub>2</sub> receptors is 11 times higher than that of dopamine.

15 Example 4 - peripheral DA<sub>2</sub> dopaminergic activity (in vitro test)

The activity of CHF 1024 and CHF 1035 on peripheral DA<sub>2</sub> dopaminergic receptors has been tested in the electrically stimulated rabbit rectococcygeus muscle.

20 Both compounds determined a dose-dependent inhibition of contraction induced by electrical stimulation and were approximately 3 times more potent than dopamine, utilized as reference compound.

In the table below the IC<sub>50</sub> values (molar concentration of drug which induces 50% inhibition of the electrically induced contraction) are reported:

	CHF 1024	CHF 1035	DOPAMINE
IC <sub>50</sub> (M)	3.73 x 10 <sup>-8</sup>	2.96 x 10 <sup>-8</sup>	9.93 x 10 <sup>-8</sup>
C.I.	3.16 - 4.36	2.14 - 3.88	4.79 - 18.21

30 (95% Confidence Interval)

The effects produced by CHF 1024, CHF 1035 and dopamine were competitively antagonized by the selective DA<sub>2</sub>-antagonist domperidone.

**Example 5 - In vivo cardiovascular effects**

5        Male albino rats (Sprague Dawley, 350-400 g) were anesthetized by sodium pentobarbital (60 mg/kg) and maintained by i.v. infusion (6 mg/h). The trachea was cannulated to facilitate spontaneous respiration and body temperature was maintained at 37°C Homoeothermic  
10      Blanket Control System (Harvard, England).

15      The right femoral artery was cannulated for arterial blood pressure measurement and left jugular vein or duodenum were cannulated for drug administration. Mean arterial pressure and heart rate were continuously monitored by pressure transducer and medium gain amplifier triggered by the ECG signal, respectively.

20      After a stabilization period of about 15 min, CHF 1024 (0.23, 0.69 and 2.3 µg/kg/min) was administered by intravenous infusion for 30 min and cardiovascular parameters were recorded for further 30 min after discontinuation.

CHF 1035 was administered intraduodenally (1 mg/kg).

25      The response to CHF 1035 was determined in the absence and in the presence of the selective β<sub>2</sub>-adrenoceptor antagonist ICI 118.551 (0.2 mg/kg i.v.) and the selective DA<sub>2</sub>-dopaminergic antagonist domperidone (0.3 mg/kg i.v.) both alone and in combination. The  
30      antagonists were administered 10 min before the i.d. drug administration.

Intravenous administration of CHF 1024 induced a dose-dependent reduction in mean arterial pressure which persists even after infusion discontinuation.

Effects induced by intravenous infusion of the 5 compound on mean arterial pressure in anesthetized rat. Mean  $\pm$  s.e.m. values (expressed as changes from basal value) are reported.

	$\mu\text{g}/\text{kg}/\text{min}$	n	min after infusion		stop	start	min after infusion
			5	30			
	i.v.						
VEHICLE	---	7	1.7±2.0	3.7±2.9	4.0±2.2	4.0±2.4	2.0±2.4
CHF 1024	0.23	6	-6.3±2.1	-13.7±4.2	-8.3±3.4	-8.0±3.3	
	0.69	6	-24.0±3.8	-25.7±5.4	-12.7±5.2	-6.7±3.3	
	2.3	6	-47.7±7.4	-48.7±5.7	-34.0±6.3	-25.3±7.1	

n = number of animals

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In spite of marked hypotension, no increase in heart rate was observed.

Analogously, intraduodenal administration of CHF 1035 at 1 mg/kg markedly reduced blood pressure without 5 affecting heart rate.

The hypotensive response was characterized by a rapid and marked fall (peak effect of about 45% reduction from basal value at 5 min after administration) followed by a slow recovery (about 20% reduction from basal value is still present 2 hours 10 after administration).

It has been shown that the peak effect is significantly reduced by pretreatment with the  $\beta_2$ -antagonist, while DA<sub>2</sub>-antagonist significantly shortened 15 the hypotensive response (the basal value is completely recovered 60 min from administration). The administration of both antagonists combined completely abolished the hypotensive response.

It has been so demonstrated that the compound is 20 active at doses considerably lower than those described by Cannon and that both  $\beta_2$ -adrenergic and DA<sub>2</sub>-dopaminergic receptors are involved in the hypotensive activity.

In particular the DA<sub>2</sub> stimulation seems to be 25 responsible of the long-lasting activity of the compound.

In order to investigate the effects of the compound both on the hemodynamic parameters and the neurohumoral pattern, a randomized double-blind study versus placebo 30 was carried out in 18 patients with a moderate congestive heart failure (class NYHA II-III).

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Each patient received on 3 consecutive days 2 active doses of CHF 1035 and 1 placebo dose.

The following hemodynamic parameters were evaluated:

- 5 - pulmonary capillary wedge pressure (PCWP) (mmHg);
- cardiac index (CI) (L/min/m<sup>2</sup>);
- stroke volume index (SVI) (ml/min/m<sup>2</sup>);
- systemic vascular resistance (SVR) (dynesecm<sup>-5</sup>);
- heart rate (HR) (bpm);
- 10 - mean blood pressure (BPm) (mmHg).

The evaluations were carried out by catheterization of the right heart (Swan-Ganz catheter), measuring the hemodynamic parameters of the tested medicament before administration or "pre-dose" (PD) and for the 300 subsequent minutes after the administration or "after-dose" (AD), every 20 minutes for the first 2 hours, then every 60 minutes.

To evaluate the effects of the compound on neurohormones, noradrenalin (NE) (pg/ml) and adrenalin (E) (pg/ml) plasmatic levels were further evaluated, before and 140 minutes after the administration of CHF 1035 and placebo, respectively.

The administration of CHF 1035 at the 3 dose levels, induced changes in the hemodynamic and 25 neurohumoral parameters as shown in the following table:

TABLE

	5 mg		10 mg		15 mg	
	PD	AD	PD	AD	PD	AD
PCWP	22±5	18±4*	20±6	16±9*	21±7	16±6*
CI	3±1	3,4±1*	2,7±1	3,4±1*	3±1	4±1*
SVI	39±12	43±11	38±7	45±10*	40±10	49±11*
SVR	1243±27	1052±265*	1382±45	1009±315*	1359±36	881±257*
HR	74±11	78±11*	70±11	76±12	74±12	80±10*
BPM	85±12	82±12	85±10	77±13*	87±11	79±12*
NE	299±135	301±156	285±244	244±88*	340±162	308±133
E	56±29	42±21*	65±42	62±44	53±25	58±24

\*: p&lt;0.05

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On the contrary, the administration of placebo induced no changes in the same parameters.

5 The results prove that CHF 1035, at the doses used in the study, induces a significant improvement in hemodynamic parameters and is characterized by a particularly favourable pharmacological profile.

Whilst a dose-related reduction in the peripheral vascular resistances is observed (respectively -15.4%; -27.0%; -35.2% for the 3 dose levels), only a relative 10 increase in heart rate occurs, which is not clinically significant.

15 The reduction in ventricular after-load, which is the expression of the decrease in the peripheral vascular resistances, induces a significant increase in the cardiac index.

Moreover the significant reduction in the pulmonary capillary wedge pressure should be stressed, which means that the medicament also induces venous vasodilation, with a consequent reduction in the left ventricle pre- 20 load.

Therefore, the general hemodynamic effect CHF 1035 can be ascribed to the peripheral vasodilating activity of the medicament, both arterial and venous.

25 This evident activity on peripheral receptors could have induced a neurohumoral hyper-reactivity, with a consequent increase in noradrenalin and adrenalin plasmatic levels, which is an undesired reaction in a pathological subject.

30 On the contrary, the results reported above prove that CHF 1035 is capable of inducing systemic vasodilation without inducing any reflected increase in

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catecholamines plasmatic levels.

The vasodilating activity of the compound derives from its receptor properties, particularly from the activity on pre-synaptic DA<sub>2</sub> and α<sub>2</sub> receptors, the stimulation of which can inhibit the catecholamine release, as it is well known.

As said before, congestive heart failure is one of the most common causes of death and disability in industrialized nations and is among the syndromes most commonly encountered in clinical practice, affecting nearly 4 millions persons in the USA and 14 millions individuals in Europe.

The current pharmacological treatment of the condition includes diuretics, angiotensin converting enzyme (ACE) inhibitors and digitalis.

There is a strong impression among the experts that the pharmacologic treatment of patients with heart failure remains suboptimal and more effective treatment is required to prevent complications and thereby reduce morbidity and mortality.

It has been demonstrated that CHF 1035 improves the clinical condition and the exercise capacity of patients with congestive heart failure when used as add-on therapy to baseline therapy with diuretics or with diuretics and ACE-inhibitors and/or with diuretics and digitalis.

It has also been shown that the pharmacodynamic effects last longer than detectable serum levels of the drug. The time course of these effects is independent of the kinetics of the drug in the body.

The effects of CHF 1035 as added therapy have been

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evaluated in patients suffering from NYHA class II-III congestive heart failure due to mild hypertension, or coronary disease, or chronic cardiomyopathy, who were on diuretics or diuretics and an angiotensin-converting 5 enzyme inhibitor.

Recruited patients were randomly assigned to added double-blind treatment with placebo or with three different doses of the study drug (5 mg, 10 mg, 15 mg).

The study therapy was started by patients on day 1 10 and proceeded until day 28 of the study.

The following parameters have been considered to determine the clinical condition of patients:

- pulmonary congestion;
- systemic congestion;
- 15 - central haemodynamics;
- regional blood flows

The functional response to the treatments has been evaluated by exertional tests, the 6-minute walking test and the 130-meter walking test.

20 CHF 1035 improved the functional and clinical condition of patients, compared to placebo.

This improvement was ostensible in terms of the NYHA functional class, exercise performance, and symptoms and signs of pulmonary and systemic congestion, 25 central haemodynamic alterations, and decreased regional/organ blood flows.

For the evaluation of clinical condition, more than 60 symptoms or signs were evaluated.

For statistical purposes scores from signs and 30 symptoms (as applicable) were summed to form clinical compound scorings (CCSs) of pathophysiological

importance in congestive heart failure.

Three CCSs were evaluated by adding the scores for certain symptoms and signs; each symptom and sign was used for only one CCS. The central hemodynamics (CH, 0-5 17), the pulmonary congestion (PC, 0-26), and the systemic congestion (SC, 0-8) CCS were associated with the NYHA functional class ( $p=0.013$ ;  $p=0.001$ ;  $p=0.001$ ) before, and they correlated with it positively ( $p=0.001$ ;  $p=0.022$ ;  $p<0.001$ ) after CHF 1035 add-on therapy.

10 The pulmonary congestion CCS correlated also with the 130-m mean walking velocity ( $p=0.002/p=0.035$ ) and with the left ventricle end-diastolic ( $p=0.026/p=0.019$ ) and end-systolic internal dimensions before/after CHF 1035 add-on therapy.

15 The pulmonary congestion appeared as the most important determinant of the functional status in congestive heart failure and was the most sensitive CCS to CHF 1035 add-on therapy.

Furthermore, pharmacological and clinicopharmacological studies showed that CHF 1035 increases diuresis 20 without affect natriuresis and kaliuresis.

CHF 1035 is the diisobutyroyl ester of 5,6-dihydroxy-2-methylaminotetralin, which is referred to as CHF 1024.

25 Immediately after the administration, CHF 1035 is transformed by the plasma and tissue esterases into the pharmacologically active desesterified form, which is also included within the present invention.

Due to these favourable characteristics, CHF 1035 30 can be advantageously used as pro-drug for the preparation of pharmaceutical compositions for the

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therapy of cardiac disorders and in particular of the congestive cardiac failure.

The daily dose of the active ingredient can vary from 1 to 100 mg and preferably will range from 2.5 to  
5 20 mg.

The administration can be performed by any route, preferably by the oral route.

For the oral administration, the compound can be formulated in solid or liquid preparations, preferably  
10 in tablets, using the additives and excipients of common use in pharmaceutical technique.

Another particularly advantageous method for the administration of the compound of the invention are the transdermal systems, which are adhesive matrixes that  
15 can be applied to the skin containing a suitable concentration of the active ingredient, which can gradually be released thus entering the blood circulation.

CLAIMS

1. The use of 5,6-diisobutyroyloxy-2-methylaminotetralin, or a pharmaceutically acceptable salt thereof, in the preparation of pharmaceutical compositions for the therapy of heart disorders, particularly congestive heart failure.
2. Pharmaceutical compositions for use in the treatment of cardiac disorders, particularly congestive heart failure, containing 5,6-diisobutyroyloxy-2-methylaminotetralin, or a pharmaceutically acceptable salt thereof, in combination with suitable excipients.
3. Pharmaceutical compositions as claimed in claims 1 and 2, characterized in that the daily dose of the active ingredient ranges from 1 to 100 mg, preferably from 2.5 to 20 mg.
4. Pharmaceutical compositions as claimed in claim 2 wherein the treatment is a method of treating cardiac heart failure and the compound is administered, in said treatment, in an amount of 1-100 mg/day and, preferably, in an amount of 2.5-20 mg/day.
5. A method of providing a treatment of cardiac disorders, particularly congestive heart failure, to a human patient, comprising administering a therapeutically effective amount of a pharmaceutical composition, as claimed in any of claims 2-4, to said human patient.
6. The use of 5,6-dihydroxy-2-methylaminotetralin, or a pharmaceutically acceptable salt thereof, as active metabolite of 5,6-diisobutyroyloxy-2-methylaminotetralin in the preparation of pharmaceutical compositions for the treatment of cardiac disorders, particularly congestive heart failure.

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# INTERNATIONAL SEARCH REPORT

Intern'l Application No  
PCT/EP 96/01060

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 6 A61K31/135 A61K31/22		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols) IPC 6 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB,A,2 123 410 (CHIESI FARMACEUTICI SPA) 1 February 1984 cited in the application ---	
A	EUR.J. PHARMACOL., vol. 81, no. 2, 1982, pages 293-299, XP000602893 J.D. KOHLI ET AL.: "Modification of cardiovascular actions of 2-amino-5,6-dihydroxytetralin by N,N-di-n-propyl substitution." ---	-/-
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		<input checked="" type="checkbox"/> Patent family members are listed in annex.
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Date of the actual completion of the international search	Date of mailing of the international search report	
4 October 1996	17.10.96	
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer  Klaver, T	

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NEUROCHEM. RES., vol. 6, no. 4, 1981, pages 365-375, XP002015115 L.E. DYCK: "Release of radiolabeled dopamine, p-tyramine and m-tyramine from rat striatal slices by some aminotetralins." -----	

**INTERNATIONAL SEARCH REPORT**Internal Application No  
PCT/EP 96/01060

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A-2123410	01-02-84	DE-A-	3320936	22-12-83



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**INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)**

<b>(51) International Patent Classification 6 :</b> <b>A61K 31/135, 31/22</b>		<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 96/29065</b> <b>(43) International Publication Date:</b> 26 September 1996 (26.09.96)
<b>(21) International Application Number:</b> PCT/EP96/01060			<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
<b>(22) International Filing Date:</b> 13 March 1996 (13.03.96)			
<b>(30) Priority Data:</b> MI95A000532 17 March 1995 (17.03.95)	IT		
<b>(71) Applicant (for all designated States except US):</b> CHIESI FARMACEUTICI S.P.A. [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT).			<b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> CHIESI, Paolo [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT). BONGRANI, Stefano [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT). RAZZETTI, Roberta [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT). CIVELLI, Maurizio [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT). UMILE, Alberto [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT).			<b>(88) Date of publication of the international search report:</b> 28 November 1996 (28.11.96)
<b>(74) Agent:</b> BIANCHETTI, Giuseppe; Studio Consulenza Brevetuale, Via Rossini, 8, I-20122 Milano (IT).			

**(54) Title:** AMINOTETRALIN DERIVATIVE FOR THE THERAPY OF CARDIOVASCULAR DISEASES

**(57) Abstract**

The use of 5,6-diisobutyroloxy-2-methylaminotetralin in the preparation of pharmaceutical compositions for the therapy of cardiac disorders, particularly of congestive heart failure.

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